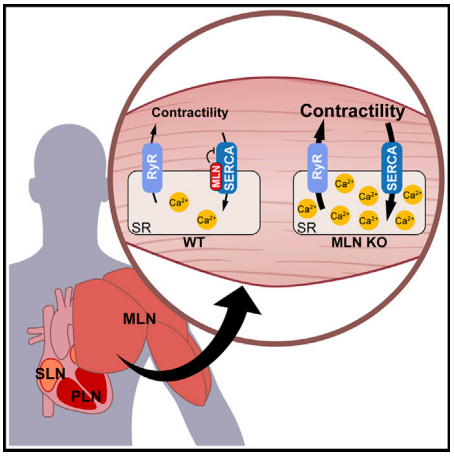
# In This Issue

Cell




## Micropeptide's Brawny Powers

PAGE 595

Anderson et al. identify a skeletal muscle-specific micropeptide called myoregulin, encoded within a long noncoding RNA, that controls skeletal muscle function by directly inhibiting the pump activity of the $^{Ca2+}$-ATPase SERCA. Mice lacking myoregulin demonstrate improved intracellular calcium handling and exercise performance.

## Gut-Level Individuality

PAGE 583

The species composition of gut microbiomes can differ markedly between individuals. Greenblum et al. now uncover extensive variation within individual gut microbial species in their gene composition and copy number and link these strain-level differences to obesity and inflammatory bowel disease.

## Decoding a Long Noncoding Mystery

PAGE 607

EBER2 is a highly abundant noncoding RNA with unknown function that is expressed by the Epstein-Barr virus. Lee et al. find that EBER2 localizes to specific repeat sites on viral chromatin to facilitate binding of its interacting host transcription factor PAX5 to these sites. Recruitment of the EBER2-PAX5 complex depends upon RNA-RNA interactions between EBER2 and nascent transcripts that together control the viral lytic cycle and infection.

## An Extracellular Stop to Influenza

PAGE 631

Interferon-stimulated genes (ISGs) act in concert to provide a tight barrier against viruses. Using a screen to identify ISGs inhibiting late stages of the influenza A virus infection, Dittman et al. find that plasminogen activator inhibitor (PAI-1) blocks maturation of the viral surface glycoprotein, thus reducing virus spread in the airways. These findings show that the innate immune system, driven by type I interferon, uses modulation of the extracellular environment to inhibit viruses.

## Stress Test for RNA

PAGE 644

The CCA-adding enzyme monitors the stability of tRNAs and tRNA-like small RNAs. Whereas CCA is added to stable RNAs, CCACCA is added to unstable ones to initiate their degradation. Kuhn et al. now characterize how these two scenarios are distinguished. Following CCA addition, stable RNAs are ejected, whereas unstable RNAs refold and are subjected to a second round of addition. Therefore, RNAs proofread themselves through differential responses to the interrogation of the enzyme.

## Switching Speed with a Squeeze

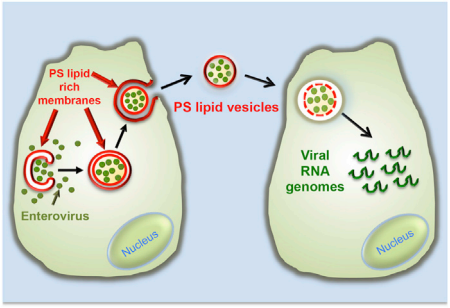
PAGE 659 and PAGE 673

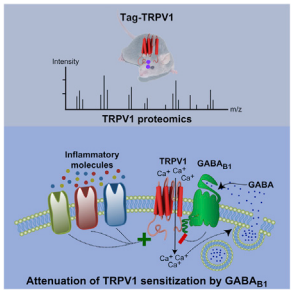
Fast amoeboid cell migration in 3D environments is central to developmental and disease-related processes, such as cancer metastasis. Liu et al. and Rupretch et al. now find that changes in the environment, namely absence focal adhesion and strong confinement, trigger the switch in motility behavior. Liu et al. analyze a large set of different slow mesenchymal cells and show that the requirements for the motility switch are universal. Rupretch et al. demonstrate that in vivo, during zebrafish development, fluctuations in cortical contraction forces act in in concert with confinement and low adhesiveness, allowing embryonic progenitor cells to acquire a fast and persistent migratory behavior.

## Viruses Gang Up

PAGE 619

A central paradigm in virology is that each virus largely behaves as an independent infectious unit. Chen et al. now demonstrate that clusters of enteroviruses are packaged within phosphatidylserine (PS)-enriched vesicles that are nonlytically released from cells. Viruses within these vesicles have enhanced infection efficiency, and PS lipids serve as cofactors for enterovirus receptors. Clustering viruses within vesicles enables multiple viral genomes to be collectively transferred into cells, facilitating genetic cooperativity among viral quasispecies and promoting viral replication.






## Curbing Pain

PAGE 759

Inflammatory pathways stimulate the capsaicin receptor TRPV1, leading to pain hypersensitivity. Hanack et al. identify a feedback mechanism that keeps TRPV1-mediated pain in check and could lead to new avenues for analgesic therapy. Release of the neurotransmitter GABA in response to TRPV1 activity triggers a noncanonical signaling pathway that inhibits only hyperactive TRPV1, leaving homeostatic pain responses intact.

## Catastrophic Cure

PAGE 686

Chromothripsis is a catastrophic cellular event, first described in cancer, in which chromosomes are shattered and pieced back together imperfectly. McDermott et al. report a remarkable case in which a woman with WHIM syndrome, an inherited immunodeficiency disease, was fortuitously cured by a chromothriptic event in a single hematopoietic stem cell that deleted the abnormal copy of the disease gene. This cell then took over the bone marrow and restored normal immune function.

## Complement-ing Tumor Suppression

PAGE 700

Macrophages have a crucial role in mediating inflammation that contributes to development of cancer. Bonavita et al. report that deficiency of PTX3, a soluble mediator that regulates Complement activity, is associated with cancer in humans and causes tumor-promoting macrophage recruitment, angiogenesis, and *Trp53* mutations in mice. Thus, PTX3 acts as a physiological extrinsic oncosuppressor inhibiting tumor generation through modulation of the activity of macrophages.

## A Malignant Energy Switch

PAGE 715

AMPK is the master regulator of cellular energy homeostasis, with tumor suppressive activity. Pineda et al. describe a widespread mechanism by which AMPK is inactivated in cancer. Cancer-specific MAGE-A3/6-TRIM28 E3 ubiquitin ligase is an oncogenic driver that ubiquitinates and degrades AMPK$\alpha$1, resulting in downregulation of autophagy and increased mTOR signaling. These findings identify the mechanism of action of the MAGE-A3/6 cancer-testis antigens and illustrate a regulatory axis for altering cellular metabolism in cancer.

## Chaotic Therapy for Cancer

PAGE 729

The ERK kinase has been long thought to be the only substrate of MEK. Tang et al. now find that HSF1, the master regulator of proteotoxic stress responses, is a new MEK substrate. MEK blockade inactivates HSF1 and provokes proteomic chaos. Tumor cells are particularly susceptible to proteostasis disruption. In fact, amyloidogenesis induced by MEK inhibition suppresses tumor growth, suggesting that disruptions of the fragile tumor proteostasis may be feasible as therapeutic strategy.

## Inflaming Metabolic Dysfunction

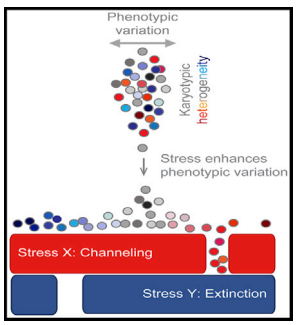
PAGE 745

A high-fat diet is associated with several metabolic abnormalities such as hyperglycemia and increased rates of hepatic glucose production. Perry et al. demonstrate that these abnormalities are primarily caused by increased macrophage-derived IL-6 levels in white adipose tissue that results in impaired lipolysis and a concomitant increase in acetyl coA levels that fuel hepatic glucose production. Inflammation, thus, is likely the underlying trigger of metabolic dysfunction associated with a high-fat diet.

## Constant Change Is the Mother of All Frustration

PAGE 785

Pathogens such as HIV and influenza are highly mutable. Their neutralization requires the generation of antibodies that cross-react with different viral strains, which it is hard to achieve. Using an in silico approach, Wang et al. find that cross-reactive antibodies occur with low probability because conflicting selection forces, imposed by the presence of different variants of the same antigen, frustrate affinity maturation. Importantly, frustration can be overcome by sequential immunization approaches.




## Conformity Quells Resistance

PAGE 771

Many diseases that readily evolve drug resistance are caused by cell populations that acquire diverse karyotypes or chromosome copy number. Chen et al. find that growth-suppressing stresses only serve to increase the heterogeneity of aneuploid populations, causing resistance to emerge. Using a fungal pathogen as a model system, the authors propose and test a strategy termed an "evolutionary trap" to eradicate such populations. One stress is applied to homogenize the population via adaptation; a second specifically targets and eliminates the new newly dominant karyotype.